REMARKS

Status of the Claims.

Claims 3, 6, 15, 58, 63 and 66-71 are pending with entry of this amendment. Claims 4-5 were canceled in the amendment filed on March 15, 2011 without disclaimer or prejudice to renewal. Claims 3, 6 and 15 are amended to change the article from "the" to "a," in accordance with the Examiner's suggestions. New claim 71 finds support, *e.g.*, on page 12, lines 13-14. No new matter is added by the present amendments, and the Examiner is respectfully requested to enter them.

35 U.S.C. §112, First Paragraph.

Claims 3-6, 15, 58, 63 and 66-70 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection for the reasons discussed in below.

According to M.P.E.P. § 2163, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Citing to*, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order

for the disclosure to satisfy the description requirement. Moreover, there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976).

Also, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. M.P.E.P. § 2164.05(a), *citing to In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). The examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims. *See, Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

Furthermore, the Federal Circuit's evolving written description precedent must be considered. Very recently, the *en banc* Federal Circuit set forth a framework for considering the written description requirement under 35 USC 112, 1st paragraph. *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 2008-1248, 2010 WL 1007369 (Fed. Cir. Mar. 22, 2010) (*en banc*).

The court wrote that

> the [written description] test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed.

The court presented "a few broad principles that hold true across all cases". Among these, it is important to recognize that "the written description requirement does not demand either examples or an actual reduction to practice." Although the court provided some general guidance about the scope and purpose of the requirement, it acknowledged that analysis of written description issues will remain highly fact-specific with few "bright line" rules. The Federal Circuit precedent should be considered

in conjunction with the specific examination guidelines presented by the USPTO, specifically its Written Description Training Materials (Revision 1, March 25, 2008).

The presently claimed invention is directed to methods for screening or selecting at least one cell expressing a polypeptide with a desired binding affinity to a ligand by providing a plurality of eukaryotic cells each comprising an expression cassette comprising a first polynucleotide encoding a polypeptide variant, at least one stop codon downstream of the first polynucleotide, and a second polynucleotide encoding a cell membrane anchoring peptide downstream of the stop codon; cultivating the cells with an aminoglycoside antibiotic; and using FACS to select at least one cell expressing the polypeptide variant fused to a cell membrane anchoring peptide based on binding affinity of said polypeptide variant to said ligand. Fundamentally, the methods provide a system that permits the efficient selection of cell lines expressing high levels of recombinant proteins by using Fluorescence-Activated Cell Sorting (FACS) and that relies on the property of aminoglycoside antibiotics to promote translational readthrough. In the presence of aminoglycosides, translational readthrough is promoted and a subset of recombinant protein is produced as the recombinant protein fused to the cell membrane anchor signal. As a result, this fusion protein is displayed at the external surface of host cells, and cells displaying high levels of membrane-anchored recombinant protein can be selected by FACS. *See*, *e.g.*, the Specification at page 8, line 28 through page 9, line 8. The claims are not directed to any particular gene, target, or pathway. Rather, they are directed to a process for selection of a cell or cells that express any desired fusion protein that is readily detectable by FACS. The claimed process contemplates that, in intermediate steps, there will be many cells that do not express the desired fusion protein, however, the step of screening using FACS readily distinguishes the cells that do from the cells that do not express the fusion protein. This is not in any way a suggestion that the claims are too broad for the associated disclosure. Rather it reflects the nature and utility of present expression and screening methods. The cells comprising an expression cassette comprising a first polynucleotide encoding a polypeptide variant, at least one stop codon downstream of the first polynucleotide, and a second polynucleotide encoding a cell membrane anchoring peptide downstream of the stop codon is part of the inventive process and is integral to its usefulness. It harnesses the benefits of controlled induction of expression of the fusion protein in the presence of an aminoglycoside antibiotic and of screening by FACS to identify the desired cells expressing the fusion protein. In view of this, *Eli Lilly*

and related cases have little relevance to the claims at issue, cited by the Examiner on page 9 of the present Office Action.

Within the context of the pending method claims, a few points should be taken. First, as the courts and the PTO have noted, the written description of the patent must be considered from the perspective of the person skilled in the art at the time of the invention. At the time of the January 30, 2004 effective filing date of the present application, FACS was a standard screening method well known to those of skill in the art for many years (*i.e.*, many decades). *See e.g.*, the Specification at page 11, lines 6-15 and present Office Action at page 23, citing to Sabbadini. Such screening permits one to quickly determine which members of a large diverse population have characteristics of interest (*i.e.*, that express the polypeptide-membrane anchoring peptide fusion in the presence of an aminoglycoside antibiotic). Additionally, the individual steps of expressing fusion proteins, cultivating eukaryotic cells and screening using FACS were well known to those of skill in the art at the time of the effective filing date of the present application.

Moreover, the specification clearly describes each of the claimed method steps in sufficient detail to clearly convey possession of the claimed invention to the person of ordinary skill in the art. Operations of 1) providing a plurality of eukaryotic cells each comprising an expression cassette comprising a first polynucleotide encoding a polypeptide variant, at least one stop codon downstream of the first polynucleotide, and a second polynucleotide encoding a cell membrane anchoring peptide downstream of the stop codon; 2) cultivating the cells with an aminoglycoside antibiotic; and 3) using FACS to select at least one cell expressing the polypeptide variant fused to a cell membrane anchoring peptide, recited in claim 3, are clearly described in various sections of the specification and further supported by knowledge in the art.

Providing a plurality of eukaryotic cells – The Specification both describes and demonstrates providing a plurality of eukaryotic cells each comprising an expression cassette comprising a first polynucleotide encoding a polypeptide variant, at least one stop codon downstream of the first polynucleotide, and a second polynucleotide encoding a cell membrane anchoring peptide downstream of the stop codon.

With respect to the first polynucleotide encoding a polypeptide variant, the Specification teaches at page 11, line 26 to page 12, line 22 that

> The polypeptide of interest is not limited to any particular protein or group of proteins, but may on the contrary be any protein, of any function or origin, which one desires to select and/or express by the methods described herein. The polypeptide of interest may thus be a therapeutic protein such as a cytokine, an antibody, a hormone or a therapeutic enzyme. Alternatively, the polypeptide of interest may e.g. be an industrial enzyme.
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> The polypeptide of interest can be a mature protein or a precursor form thereof, or a functional fragment thereof that essentially has retained a biological activity of the mature protein.
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> The polypeptide can be a therapeutic polypeptide useful in human or veterinary therapy, i.e. a polypeptide that is physiologically active when introduced into the circulatory system of or otherwise administered to a human or an animal; a diagnostic polypeptide useful in diagnosis; or an industrial polypeptide useful for industrial purposes, such as in a manufacturing process where the polypeptide constitutes a functional ingredient or where the polypeptide is used for processing or other modification of raw ingredients during manufacturing.
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> The polypeptide can be of mammalian origin, e.g. of human, porcine, ovine, ursine, murine, rabbit, donkey, or bat origin, of microbial origin, e.g. of fungal, yeast or bacterial origin, or can be derived from other sources such as from venom, or from a leech, frog or mosquito. In the case of a therapeutic polypeptide, this is preferably of human origin, while an industrial polypeptide of interest is often of microbial origin.
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> Specific examples of groups of polypeptides that may be selected or expressed according to the invention include: an antibody or antibody fragment, a plasma protein, an erythrocyte or thrombocyte protein, a cytokine, a growth factor, a profibrinolytic protein, a binding protein, a protease inhibitor, an antigen, an enzyme, a ligand, a receptor, and a hormone. Of particular interest is a polypeptide that mediates its biological effect by binding to a cellular receptor when administered to a patient. In the case of an antibody, this can be a polyclonal or monoclonal antibody, and can be of any origin including human, rabbit and murine origin. Preferably, the antibody is a human or humanized monoclonal antibody. Specific antibodies and fragments thereof include those reactive with any of the therapeutic non-antibody proteins mentioned below.

The Specification further describes in detail on page 12, line 25 through page 16, line 26 examples of when the polypeptide variant encoded by the first polynucleotide is an antibody. Detailed examples of when the polypeptide variant encoded by the first polynucleotide is a non-antibody polypeptide is further described on page 16, line 29 through page 18, line 18. Based on the teachings of the specification, the particular structure of the polypeptide variant encoded by the first polynucleotide is not critical to practicing the present methods. In addition to describing numerous representative examples of polypeptide variants that can be encoded by the first polynucleotide, Applicants also provide several working examples. The Examiner acknowledges that the specification describes in Example 10 on pages 45-47 a method for screening and selecting mammalian cells for monoclonal antibody by FACS-based enrichment. Page 4 of the present Office Action. The Examiner alleges that the disclosure describes only mAb libraries in a retroviral vector with the stop codon that binds to antigen. Page 4 of the present Office Action. This is incorrect. In addition to demonstrating the present methods for screening antibodies (Example 10 and Figures 19 and 20), the Specification provides working examples demonstrating the construction of vectors and using FACS to screen for soluble or membrane-bound fusion protein where the polypeptide variant is, *e.g.*, protein C (Examples 1-3 and 6, and Figures 1-6, 8 and 14-16); Factor VII (Examples 4, 7 and 9, and Figures 9, 11-13, 17, 22 and 23); interferon-α (Example 5 and Figures 7 and 18); or Adiponectin receptor 1 (Example 8 and Figure 10).

With respect to the at least one stop codon, the Specification teaches at page 1, lines 12-13 and on page 18, lines 21-23 that the stop codon used in the method can be any of the three stop (nonsense) codons UAA, UGA and UAG in eukaryotic host cells. The Specification describes regulated readthrough approaches in detail on page 18, line 20 through page 28, line 15. The Specification teaches that readthrough levels can be adjusted by selection of a suitable stop codon and the tetranucleotide context of the stop codon. Page 18, line 23 through page 19, line 4. Specific differences in using the UGA versus the UAA stop codons and in different tetranucleotide contexts are discussed in the Specification, *e.g.*, at page 22, lines 17-33. Additionally, the Specification provides working examples of using the UGA (Examples 1-2 and 5, and Figures 3, 7, 16, 18 and 19) and UAA (Examples 1-4 and 6-9, and Figures 2, 5-6, 8-11, 13, 15, 17 and 21-23) stop codons in different tetranucleotide contexts. As acknowledged by the Examiner, further guidance regarding the

differences in using the UAA, UGA or UAG stop codons and in different tetranucleotide contexts is provided by Manuvakhova, *et al.*, *RNA* (2000):1044-1055. *See*, pages 23-24 of the present Office Action.

With respect to the plurality of eukaryotic cells, the Specification teaches on page 25, lines 11-14 that the present invention is applicable to any type of host cell from organisms in which translational stop codon readthrough is promoted in the presence of aminoglycosides, in particular eukaryotic cells such as mammalian cells or other animal cells, filamentous fungal cells, yeast cells, insect cells and transgenic plants and animals. Specific examples of suitable eukaryotic host cells are described on page 25, lines 14-25. Prokaryotic host cells are notably not listed.

The Examiner expresses concern that there are differences in the degree of suppression amongst different stop codons in difference mRNA contexts and in different eukaryotic host cells. Pages 5-6 of the present Office Action. Applicants respectfully remind the Examiner that this is a written description rejection and not an enablement rejection. Regardless, at the time of the January 30, 2004 effective filing date of the present application, information published in the prior art provided guidance to those of ordinary skill in the art how achieve a desired level of stop codon readthrough and how to avoid inoperable embodiments. For example, Manuvakhova, *et al.*, *RNA* (2000) 6:1044-55, cited by the Examiner in the present Office Action, provides information on the different levels of stop codon readthrough in an *in vitro* rabbit reticulocyte translation assay for all three eukaryotic stop codons (*i.e.*, UGA, UAG and UAA) in the context of different iterations of tetranucleotides. Figure 2 on page 1047 of Manuvakhova. As the Examiner points out, Welch also provides the skilled person with information on which codon to use in particular contexts and with particular host cells. Pages 5-6 and 9 of the present Office Action. A specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. M.P.E.P. § 2164.05(a).

Cultivating – With respect to the step of cultivating the cells in a presence of an amino glycoside antibiotic under conditions that allow expression of the polypeptide variant, the Specification teaches on page 27, line 24 that in production methods of the present invention, cells are cultivated in a nutrient medium suitable for production of the polypeptide in question using methods known in the art. For example, the cells may be cultivated by shake flask cultivation, small-scale or large-scale

fermentation (including continuous, batch, fed-batch, or solid state fermentations) in laboratory or industrial fermenters performed in a suitable medium and under conditions allowing the polypeptide to be expressed and/or isolated. The cultivation takes place in a suitable nutrient medium comprising carbon and nitrogen sources and inorganic salts, using procedures known in the art. Suitable media are available from commercial suppliers or may be prepared according to published compositions (e.g., in catalogues of the American Type Culture Collection). When the polypeptide is secreted into the nutrient medium, the polypeptide can be recovered directly from the medium. The Specification discussed exemplary aminoglycoside antibiotics on page 22, lines 6-10. Accordingly, this step utilizes techniques and aminoglycoside antibiotics well known to those of skill at the time of the effective filing date of the application.

Using FACS to select – With respect to the step of using FACS to select at least one cell expressing the polypeptide variant fused to a cell membrane anchoring peptide based on binding affinity of said polypeptide variant to said ligand, the Specification teaches on page 28, lines 3-6, that selection or screening of polypeptides according to the methods of the invention may be performed by any suitable means, e.g. by FACS in the case of membrane bound polypeptides or by suitable detection of a reporter peptide or epitope tag. The Specification further demonstrates the use of FACS for screening and selecting, *e.g.*, in Examples 2-6 and 8-10, and Figures 4, 5, 6, 8, 12 and 13. FACS or flow cytometry was a screening methodology widely used and well-known to those of skill in the art at the time of the effective filing date of the present application. The Examiner acknowledges on page 23 of the present Office Action that at the time the invention was made, FACS was a conventional way of screening or sorting out cells from a pool or library, citing to U.S. Patent No. 7,183,105 ("Sabbadini").

It is respectfully submitted that the person of skill in the art would readily understand the claimed invention and appreciate that Applicants did in fact invent it. For at least these reasons, the rejection should be withdrawn.

The Examiner premises the written description rejection, in part, on an alleged failure of the specification to set forth a sufficient number of examples or other concrete identifying characteristics of the Applicants' "claimed genus." In this regard, the Examiner relies on *Eli Lilly v. University of California*:

> To satisfy a written description requirement for a claimed genus a sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Along these lines, the Examiner states:

> A written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials. University of California v. Eli Lilly, 43 USPQ 2d 1398, 1405(1997).

Office Action at the bottom of page 9. However, unlike the *Eli Lilly* case cited by the Examiner, the particular polypeptide variant is not critical to practicing the present methods. The difficulty with the claims at issue in *Eli Lilly* and similar cases was that the claims covered specific compounds or classes of compounds, rather than a structurally agnostic method, such as the methods claimed in the present invention. The claimed invention is directed to a process in which patentability resides in the sequence of method operations. See Example 16 ("Process Claim Where Novelty Resides In The Process Steps") of the USPTO's Written Description Training Materials, Revision 1 (March 25, 2008).

The Examiner also cites to *Superguide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004) ("Superguide") and M.P.E.P. § 2111.01(II) for the proposition that a particular embodiment appearing in the Written Description may not be read into a claim when the claims language is broader than the embodiment. Page 12 of the present Office Action. It appears that the Examiner has cited this case and M.P.E.P. section out of context and is attempting to do exactly what the Court is proscribing. As Applicants understand M.P.E.P. § 2111.01(II), Superguide is discussed along with *Liebel-Flarsheim Co. v. Medrad Inc.*, 358 F.3d 898, 906, 69 USPQ2d 1801, 1807 (Fed. Cir. 2004) and *Altiris Inc. v. Symantec Corp.*, 318 F.3d 1363, 1371, 65 USPQ2d 1865, 1869-70 (Fed. Cir. 2003) for the proposition that even if the Specification discloses a single embodiment, it is improper to

construe the claims as being limited to that embodiment. Even though the present Specification provides numerous working embodiments, discussed above, the Examiner appears to be requiring that Applicants limit the claims to the demonstrated embodiments, which is exactly what the Court has expressly rejected.

The Examiner further cites to *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005) ("Capon") for the rule that the written description requirement implements the principle that a patent must describe the technology that is sought to be patented. Page 12 of the present Office Action. The Examiner appears to have cited the rule stated in this case without considering the facts and holding of the case. The inventions in Capon were directed to chimeric genes comprising known nucleic acid sequences. Capon at 1351-1354. Following recitation of the statutory requirements for written description, the Court disagreed with the analysis of the Board of Patent Appeals and Interferences (BPAI), stating that

> For the chimeric genes of the Capon and Eshhar inventions, the law must take cognizance of the scientific facts. The Board erred in refusing to consider the state of the scientific knowledge, as explained by both parties, and in declining to consider the separate scope of each of the claims. None of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e., *Regents v. Lilly, Fiers v. Revel, Amgen*, or *Enzo Biochem*, require a re-description of what was already known.

Capon at 1357. Capon further supports Applicants position that the holding of *Eli* Lilly is inapposite to the present invention. The Court provided further reasons for disagreeing with the opinion of the BPAI, stating that

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh.
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> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also

> evolves between what is known and what is added by each inventive contribution. Both Eshhar and Capon explain that this invention does not concern the discovery of gene function or structure, as in Lilly. The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.

Capon at 1358. Like the inventions of Capon and Eshhar, the present methods utilize conditionally induced chimeras of known polynuceotide and known polypeptide sequences by inducing stop codon readthrough in the presence of an aminoglycoside antibiotic. Accordingly, like in Capon, it is not necessary for Applicants to reiterate the nucleotide sequences of the first and second polynucleotides used in the present methods.

With respect to claim scope, the Court in Capon stated

> It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. See *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976) ("The examples, both operative and inoperative, are the best guidance this art permits, as far as we can conclude from the record"). While the Board is correct that a generic invention requires adequate support, the sufficiency of the support must be determined in the particular case. Both Eshhar and Capon present not only general teachings of how to select and recombine the DNA, but also specific examples of the production of specified chimeric genes.

Capon at 1359. Like in Capon, and as discussed above, the present Specification provides both general guidance regarding how to practice each of the steps of the claimed method (*e.g.*, on pages 11-28) and numerous specific working examples of inducing expression of membrane-bound fusion proteins in the presence of an aminoglycoside antibiotic and selecting for cells expressing membrane bound fusion protein using FACS (*e.g.*, Examples 1-10 and Figures 1-23). The Specification provides ample guidance for several representative operable embodiments. The prior art, including references cited by the Examiner, provides guidance for avoiding inoperable embodiments.

In most ways, the structure of any particular protein is irrelevant to the pending claims. Rather, it is an improved strategy for efficiently screening for cells that express a desired polypeptide with a desired binding affinity to a ligand that is relevant to the pending claims. As explained in the instant specification, the identities of the polypeptide expressed by the first polynucleotide are not particularly relevant to the inventive method. See, *e.g.*, the Specification at pages 12 through 18.

As mentioned, the claimed methods involve screening a diverse population of eukaryotic cells using FACS. It is fully expected and understood that many of the screened cells will not express or only express low or non-detectable levels of membrane-bound fusion protein, even in the presence of an aminoglycoside antibiotic. Applicants are not claiming that they invented a way to identify which polypeptide variants will have a desired binding affinity to a ligand. Rather, they invented a way to conveniently and efficiently screen for cells that conditionally express a polypeptide with a desired binding affinity to a ligand in membrane-bound form when the cells are cultivated in the presence of an aminoglycoside antibiotic.

Lastly, the Examiner is invited to consider certain points made in Example 16 ("Process Claim Where Novelty Resides In The Process Steps") of the USPTO's Written Description Training Materials, Revision 1 (March 25, 2008). Importantly, the PTO points to the following factors militating in favor of a conclusion that a biotechnology process claim (and associated specification) meets the written description requirement:

1. All chemicals used in the disclosed method are known in the art.

2. The level of skill and knowledge in the art is such that those skilled in the art know of numerous nucleic acids that could potentially be used in the claimed method.

3. While the sequences of the nucleic acids usable in the claims are not disclosed in the specification, a patent application is not required to reproduce knowledge that is available in the art.

4. The degree of predictability within the claimed genus is high. Each of the disclosed manipulations is well known in the art and disclosed in the specification.

For at least the foregoing reasons, Applicants have demonstrated possession of the claimed invention. Accordingly, withdrawal of the written description rejection is respectfully requested.

35 U.S.C. §112, Second Paragraph.

Claims 3-6, 15, 58, 63 and 66-70 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

1. The Examiner objected to the recitation of "the presence of a termination suppression agent" in claim 3, step b). Without agreeing with or acquiescing to the Examiner's position, and solely in the interest of furthering prosecution, Applicants have amended claim 3, step b) to recite "a presence of a termination suppression agent."

2. The Examiner objected to recitation of "the surface of said cell" in claim 6. Without agreeing with or acquiescing to the Examiner's position, and solely in the interest of furthering prosecution, Applicants have amended claim 6 to recite "a surface of said cell."

3. The Examiner objected to claim 15 for reciting "the absence of a termination suppression agent." Without agreeing with or acquiescing to the Examiner's position, and solely in the interest of furthering prosecution, Applicants have amended claim 15 to recite "an absence of a termination suppression agent."

In view of the amendments to the claims, the Examiner is respectfully requested to withdraw this rejection.

35 U.S.C. §102.

Claims 3-6, 15, 58, 63 and 66-70 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 7,191,257 ("Hoogenboom"). This rejection is traversed for the reasons discussed below.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). M.P.E.P. § 2131. Because the hallmark of anticipation is prior invention, the prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements "arranged as in the claim." *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed.Cir. 1983). A reference that discloses all of the claimed ingredients, but not in the order claimed, would not anticipate, because the reference would be missing any disclosure of the limitations of the claimed invention "arranged as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F. 3d 1359, 1370 (Fed.Cir. 2008). The test for the meaning of the expression "arranged as in the claim" is thus more accurately understood to mean "arranged or combined in the same way as in the claim. *Id. See also*, *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452 (Fed.Cir.1984), *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361 (Fed.Cir. 2000), and *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323 (Fed.Cir. 2008). The Federal Circuit has repeatedly held that unless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F. 3d at 1371. It is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention. *Id*, *quoting In re Arkley*, 59 C.C.P.A. 804, 455 F.2d 586, 587 (1972).

Claims 3-6, 15, 58, 63 and 66-69

Claim 3, the only pending independent claim, recites the steps of:

> a) providing a plurality of eukaryotic cells each comprising an expression cassette comprising a first polynucleotide encoding a polypeptide variant, at least one stop codon downstream of the first polynucleotide, and a second polynucleotide encoding a cell membrane anchoring peptide downstream of the stop codon;

> b) cultivating the cells in the a presence of a termination suppression agent under conditions that allow expression of the polypeptide variant, wherein the termination suppression agent is an aminoglycoside antibiotic; and
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> c) using FACS to select at least one cell expressing the polypeptide variant fused to a cell membrane anchoring peptide based on binding affinity of said polypeptide variant to said ligand.

Claims 4-6, 15, 58, 63 and 66-69 depend directly or indirectly from claim 3 and therefore require performing all of the steps recited in claim 3.

In attempting to formulate the present rejection, and re-assemble the steps of the present methods within the cited Hoogenboom reference, the Examiner points to several disparate passages of Hoogenboom, in particular, column 4, line 20+ and Figure 9. Page 16 of the present Office Action.

Hoogenboom does not anticipate the present methods because in no instance does this patent teach or suggest all of the recited steps of the present methods, in one cohesive or several disconnected passages.

In the passage at column 4, lines 20-39, Hoogenboom discloses the following:

> Another element of the invention useful for control of the production is placing expression of different variable regions under control of different elements such as promoters, (trans) activators, enhancers, terminators, anti-repressors, repressors, and the like. These control elements may be inducible or repressible. Thus, the production of variable regions can be regulated, thus optimizing pairing conditions as desired. Different combinations of variable regions can be made by separation in time of expression of various variable regions and/or ratios between different paired variable regions may be manipulated by regulating expression levels. Variations are described in the detailed description. The invention also provides an expression system for carrying out a method according to the invention, comprising nucleic acids encoding variable regions together with all elements required for gene expression and pairing, preferably such an expression system comprises at least one recombinant cell, such as a bacterium, a yeast cell, a fungal cell, an insect cell, a plant cell or another eukaryotic cell, in particular, a mammalian cell, more in particular, a human cell.

In the legend for Figure 9, at column 8, lines 21 to 27, Hoogenboom states as follows:

> FIG. 9: Screening antibody mixtures produced by the same host cell for optimal bio-activity. Mixtures are made by transfecting heavy chain genes encoding the antibodies of interest (here number is 10) together with optimally paired light chain, followed by cloning of cell lines, selecting stably producing cell lines, and eventually screening the resulting antibody mixtures for optimal bio-activity.

These passages do not in any way disclose or suggest any of the steps set forth in claim 3. Although the passage at column 4, lines 20-39 may provide general guidance for controlling production of antibody variable regions, and the passage at column 8, lines 21-27 discusses screening antibody mixtures, neither cited passage teaches or suggests 1) a plurality of eukaryotic cells each comprising an expression cassette comprising a first polynucleotide encoding a polypeptide variant, at least one stop codon downstream of the first polynucleotide, and a second polynucleotide encoding a cell membrane anchoring peptide downstream of the stop codon; 2) cultivating the cells in the a presence of an aminoglycoside antibiotic under conditions that allow expression of the polypeptide variant; and 3) using FACS to select for cells expressing the polypeptide variant fused to a cell membrane anchoring peptide.

Moreover, in the passages of Hoogenboom that discuss using a stop codon, *e.g.*, in the legend of Figure 24 at column 10, lines 8-24; and in Example 17 at columns 74-76, it is not in the context of using stop codon readthrough to induce conditional expression of a fusion polypeptide in the presence of an aminoglycoside antibiotic. Instead, Hoogenboom introduces a stop codon into complementary determining regions (CDRs) of an antibody variable region as a strategy for directed mutagenesis. According to Hoogenboom, the so-called Kunkel mutagenesis method is used. One codon in a CDR is replaced with a TAA stop codon and then mutagenic oligonucleotides designed to simultaneously repair the stop codons and introduce mutations at the designed sites are used. Hoogenboom at column 74, lines 40-56. *See also*, Hoogenboom at column 75, line 41 through column 76, line 31 and at column 10, lines 14-21. In the methods of the present invention, the stop codon is retained in the expression cassette and cultivation conditions in the presence of an aminoglycoside antibiotic are employed to induce readthrough and expression of the fusion polypeptide with the membrane anchoring peptide. By contrast, in the methods of Hoogenboom, the stop codon is introduced for the purposes of a targeted site for directed mutagenesis. The introduced stop codon is

not retained but repaired simultaneously with the introduction of a mutation at the designed site. *See*, Hoogenboom at column 74, lines 48-54 and at column 75, lines 41-47 and at column 76, lines 26-31.

To the extent that Hoogenboom mentions use of an aminoglycoside antibiotic, it is only in the context of selection of successfully transfected cells, not for the purposes of inducing readthrough expression. *See*, Hoogenboom at column 33, lines 16-25; in Example 3 at column 50, lines 23-25; in Example 10 at column 60, lines 36-51 and in Example 16 at column 69, line 63 to column 70, line 10. To the contrary, once successfully transfected cells are selected and expanded into T25 flasks, Hoogenboom reports discontinuing the addition of G418 to the culture medium. *See*, Hoogenboom at column 60, lines 49-51 and at column 70, lines 8-12.

Claim 66

The Examiner attempts to further formulate an anticipation rejection against claim 66 by pointing to two additional passages of Hoogenboom at column 10, lines 8-24 and at column 13, lines 15-46, both disconnected from the passages cited above. Pages 17-19 of the present Office Action.

First, Applicants respectfully remind the Examiner that claim 66 depends from claim 3, and therefore requires all of the steps recited in claim 3. Furthermore, the additional passages from Hoogenboom identified by the Examiner do not teach or suggest all of the recited steps of the present methods, either in one cohesive passage or in several disconnected passages.

The legend for Figure 24, at column 10, lines 8-24 of Hoogenboom reads as follows:

> FIG. 24: Plasmid p2Fab-HER2 used for the identification of a light chain variable region that is pairing-compatible with two HER2-binding antibodies, h4D5v8, and 2C4. The black box is a schematic depiction of the histidine tag (six Histidines); other C-terminal-based tags are also indicated. S, signal sequence; rbs, ribosome binding site; AMP.sup.r, ampicillin resistance gene (beta-lactamase). The version of the VL of h4D5 that is present in this vector carries two designed mutations in two CDR residues, and a stop codon (indicated with *) in the CDR2 region. By site-directed mutagenesis, the CDR2 is diversified using an oligonucleotide (designed according to approach HYB2) that simultaneously removes the stop codon as well as introduces diversity at three positions of the CDR2. This plasmid directs the expression of two antibody heavy chains (as Fd chains) and one antibody light chain, and

thus allows simultaneous production, and individual detection, of two Fab fragments.

In the passage at column 13, lines 15-46, Hoogenboom reports as follows:

> Antibodies or antibody fragments can also be isolated using display-based antibody library technology, wherein antibody fragments are selected by exposing a library of such antibodies displayed on the surface of phage, yeast or other host cell, to the antigen of interest, and isolating those antibody fragments which bind to the antigen preparation. A display library is a collection of entities; each entity includes an accessible polypeptide component and a recoverable component that encodes or identifies the peptide component. Many antibody fragments have been displayed on the surface of entities that carry the genetic material encoding the antibody fragment inside the entity, such as bacteriophages. This format is termed "phage display." Phage display is described, for example, in Ladner et al., U.S. Pat. No. 5,223,409; Smith (1985) *Science* 228:1315-1317. Other display formats utilize peptide-nucleic acid fusions. Polypeptide-nucleic acid fusions can be generated by the in vitro translation of mRNA that includes a covalently attached puromycin group, e.g., as described in Roberts and Szostak (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94:12297-12302, and U.S. Pat. No. 6,207,446. The mRNA can then be reverse transcribed into DNA and cross-linked to the polypeptide. In still another display format the library is a cell-display library. Proteins are displayed on the surface of a cell, e.g., a eukaryotic or prokaryotic cell. Exemplary prokaryotic cells include *E. coli* cells, *B. subtilis* cells, spores, exemplary eukaryotic cells include yeast such as *Saccharomyces cerevisiae, Hansenula polymorpha, Pichia pastoris, Kluyveromyces lactis*, insect cells and mammalian cells. Methods for the display of antibody fragments and the construction of antibody libraries in a variety of formats are well described in the literature and known to those skilled in the art.

Like the passages cited above, the passages of Hoogenboom at column 10, lines 8-24 and at column 13, lines 15-46 do not teach or suggest 1) a plurality of eukaryotic cells each comprising an expression cassette comprising a first polynucleotide encoding a polypeptide variant, at least one stop codon downstream of the first polynucleotide, and a second polynucleotide encoding a cell membrane anchoring peptide downstream of the stop codon; 2) cultivating the cells in the a presence of an aminoglycoside antibiotic under conditions that allow expression of the polypeptide variant; and

3) using FACS to select for cells expressing the polypeptide variant fused to a cell membrane anchoring peptide.

Claim 3 and 66-67

The Examiner further points to Example 17 of Hoogenboom in attempting to formulate an anticipation rejection against claims 3 and 66-67. Hoogenboom's use of a stop codon in Example 17 for the purposes of directed mutagenesis, rather than for use in conditionally inducing expression of a fusion polypeptide in the presence of an aminoglycoside antibiotic, is discussed above.

Claim 15

The Examiner further points to Example 19 of Hoogenboom in attempting to formulate an anticipation rejection against claim 15. Applicants respectfully remind the Examiner that claim 15 depends from claim 3, and therefore requires all of the steps recited in claim 3. Furthermore, Example 19 of Hoogenboom does not mention anything about a stop codon, and therefore does not teach or suggest anything regarding the inclusion of a stop codon placed in between the nucleic acid encoding VEGF-R2 and the nucleic acid encoding alkaline phosphatase (AP) to allow for the conditional induction of a VEGF-R2-AP fusion protein in the presence of an aminoglycoside antibiotic. Finally, Hoogenboom reports that the VEGF-R2-AP fusion protein is soluble. Hoogenboom at column 80, line 52. That is, AP is not a cell membrane anchoring peptide.

Claim 63

Finally, the Examiner further points to column 32, line 63 through column 33, line 35 of Hoogenboom in attempting to formulate an anticipation rejection against claim 63. Applicants respectfully remind the Examiner that claim 63 depends from claim 3, and therefore requires all of the steps recited in claim 3. The passage of Hoogenboom at column 32, line 63 through column 33, line 35 reads as follows:

> Mammalian expression vectors will comprise an origin of replication, a suitable promoter and also any necessary ribosome-binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking non-transcribed sequences. Expression regulatory sequences may comprise promoters, enhancers,

> scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of the sequences. Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting, including polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the protein, or other sequences which alter or improve the function or stability of protein or RNA molecules. In addition to the nucleic acid sequence encoding the diversified immunoglobulin domain, the recombinant expression vectors may carry additional sequences, such as sequences that regulate replication of the vector in host cells (e.g., origins of replication) and selectable marker genes. The selectable marker gene facilitates selection of host cells into which the vector has been introduced (see e.g., U.S. Pat. Nos. 4,399,216, 4,634,665 and 5,179,017). For example, typically the selectable marker gene confers resistance to drugs, such as G418, hygromycin or methotrexate, on a host cell into which the vector has been introduced. Preferred selectable marker genes include the dihydrofolate reductase (DHFR) gene (for use in $dhfr^-$ host cells with methotrexate selection/amplification) and the neo gene (for G418 selection).

This passage says absolutely nothing regarding the inclusion of a stop codon or translational termination sequence. As discussed above, this passage expressly describes using a selectable marker gene which confers resistance to drugs to facilitate selection of host cells into which the vector has been introduced. This passage does not teach or suggest use of a stop codon placed between a nucleic acid encoding a polypeptide variant and a nucleic acid encoding a cell membrane anchoring peptide to induce conditional expression of a fusion protein comprised of the polypeptide variant and the cell membrane anchoring peptide in the presence of an aminoglycoside antibiotic.

For at least the foregoing reasons, Hoogenboom does not anticipate the claimed methods. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

35 U.S.C. §103(a).

Claims 3-6, 15, 58, 63 and 66-70 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of U.S. Patent Publ. No. 2007/0105093 ("Ciceri") or U.S. Patent No. 5,770,356 ("Light") in view of Manuvakhova, *et al.*, *RNA* (2000) 6:1044-55 ("Manuvakhova), U.S. Patent No.

7,183,105 ("Sabbadini"), and Hoogenboom, if necessary. This rejection is respectfully traversed for the reasons discussed in the previous response and below.

The Examiner has the burden of presenting a *prima facie* case of obviousness. For an invention to be obvious under 35 U.S.C. § 35 U.S.C. §103(a) requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. Indeed, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *See*, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Moreover, if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. M.P.E.P. § 2143.01(V), *citing to In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Also, if a proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. M.P.E.P. § 2143.01(VI), *citing to In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Additionally, a prior art reference must be considered in its entirety, *i.e.*, as a <u>whole</u>, including portions that would lead away from the claimed invention. M.P.E.P. § 2141.02(VI), *citing to W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (emphasis in original).

<u>The Proposed Modifications to the Primary Cited References Improperly Changes Their Principle of Operation and Renders Their Methods Unsatisfactory for Their Intended Purpose</u>

In attempting to formulate the present obviousness rejection, the Examiner cites as primary references, Ciceri and Light, which disclose methods specific to phage display. *See*, abstract and claims of Ciceri and Light. The Examiner acknowledges the neither Ciceri nor Light teach using an aminoglycoside antibiotic (*e.g.*, G-418) as suppressor agent, screening cells by FACS, or conditionally expressing a fusion protein with a cell membrane anchoring peptide (*e.g.*, a GPI anchor). Page 23 of the present Office Action. Applicants also note that neither Ciceri nor Light disclose or suggest providing a population of eukaryotic cells. This is because phage display requires using prokaryotic host cells. Yet the Examiner makes the unreasoned conclusion that it would have been

obvious to use FACS to screen cells based on the disclosure of Sabbadini, to use an aminoglycoside antibiotic as the suppressor agent in the method of Ciceri, based on the disclosure of Manuvakhova, to use a GPI anchor peptide in the method of Light or Ciceri, based on the disclosure of Sabbadini, or to employ eukaryotic host cells, based on the disclosure of Hoogenboom. Page 24 of the present Office Action.

The combination of references proposed by the Examiner in an attempt to arrive at the present invention improperly and radically changes the principle of operation of the primary cited references, Ciceri and Light. The combination of references proposed by the Examiner also renders the methods of Ciceri and Light unsatisfactory for their intended purpose. The methods of Ciceri and Light are specifically designed for use with phage display. The Examiner's proposed combination requires the substitution of a prokaryotic host cell with a eukaryotic host cell, the substitution of use of a termination suppression tRNA with an aminoglycoside antibiotic, the substitution of a fusion protein to a phage coat protein with a cell membrane anchoring peptide (*e.g.*, a GPI anchor), and the introduction of screening by FACS. There is absolutely no reason for the methods of either Ciceri or Light to employ eukaryotic host cells, because phages are cultivated in infected prokaryotic host cells. Moreover, FACS is not a methodology amenable to screening phage and aminoglycoside antibiotics are not generally appropriate for selection of prokaryotic cells. For example, WO 2003/014361 reports that G418 distinguishes between prokaryotic and eukaryotic ribosomes. WO 2003/014361 at page 7, lines 7-8 of fourth full paragraph.[1] Also, successful phage display of the fusion constructs of Ciceri and Light requires fusion to a phage coat protein.

The Examiner's proposed modifications to Ciceri and Light in an attempt to render the present methods obvious effectively change nearly every aspect of the methods of the primary references. As Applicants understand the present obviousness rejection, the Examiner has attempted to arrive at the present methods by assembling subordinate references using the disclosure of the present Specification as a guide, thereby rendering the methods of the primary cited references unrecognizable to their original principal of operation and unsatisfactory to their original intended purposes.

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[1] WO 2003/014361 was submitted with the IDS on October 30, 2007.

For at least the forgoing reasons, there is no motivation combine the cited references and modify the methods of Ciceri or Light by combining with the disclosures of Manuvakhova, Sabbadini and Hoogenboom. To do so improperly changes the principle of operation of Ciceri and Light and renders their methods unsatisfactory for their intended purposes. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Conclusion

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 267-4117.

Weaver Austin Villeneuve & Sampson LLP
500 12th Street, Suite 200
Oakland, CA 94607
Tel: (510) 663-1100
Fax: (510) 663-0920

Respectfully submitted,

/Jennifer L. Wahlsten/

Jennifer L. Wahlsten
Reg. No: 46,226